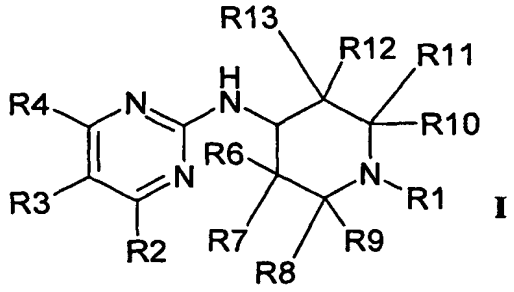
CLAIMS

1. compound of formula I or a pharmaceutically acceptable salt, ester or prodrug thereof



I

wherein

R1 is H or optionally substituted (lower alkyl, aryl or aryl-lower alkyl, heterocycloalkyl or heterocycloalkyl-lower alkyl, -C(O)-Rx, -S(O)-Rx, -$S(O)_2$-Rx, -CH_2-O-Rx or –NH-C(O)-Rx

where Rx is OH, lower alkoxy, aryloxy, aryl-lower alkoxy, or NH_2 optionally mono- or disubstituted by lower alkyl, aryl, aryl-lower alkyl, heterocycloalkyl or heterocycloalkyl-lower alkyl);

R2 is optionally substituted aryl, wherein aryl is not 4-(4-flurophenyl)-1(1-methylpiperdin-4-yl)imidazole;

each of R3 and R4 is independently H, or optionally substituted lower alkyl, CN, halo, hydroxy, lower alkoxy

Each of R6 to R13 is independently H or optionally substituted (lower alkyl, lower alkoxy, -CH_2-O-Rx, -C(O)-Rx, -O-C(O)-Rx, -S(O)-Rx, -O-S(O)-Rx, -O-S(O)-Rx, -CH_2-O-Rx or –NH-C(O)-Rx,

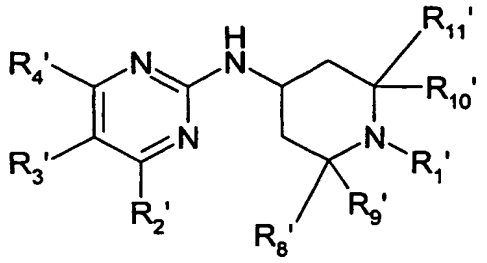
where Rx is as defined above), and

wherein at least 1 of the substituents R6 to R13 is not equal to H,or

Any pair of R6 to R13 are joined to form an optionally substituted C_1 to C_4 bridge in which one or more of the bridge atoms is optionally replaced by O, S or NRy, where Ry is H or optionally substituted (lower alkyl, -CH_2-O-Rx, -C(O)-Rx, -S(O)-Rx, -$S(O)_2$-Rx, -CH_2-O-Rx or –NH-C(O)-Rx

where Rx is as defined above).

2. A compound according to claim 1, of formula II



II

wherein

R1' is H, OH, -C(O)-Rx, -S(O)-Rx, -S(O)$_2$-Rx or -CH$_2$-O-Rx, where Rx is as defined above or optionallky substituted lower alkyl, wherein the optional substituents are preferably one or two substituents selected from OH, lower alkoxy, aryl, CN or NH$_2$ optionally mono- or disubstituted by lower alkyl, aryl, aryl-lower alkyl, heterocycloalkyl or heterocycloalkyl-lower alkyl;

R2' is optionally substituted phenyl, or heteroaryl, conveniently containing from 3 to to 10 ring members, including fused ring heteroaryl, e.g. optionally substituted pyrrole, thiophene, benzothiophene, tetrahydrobenzothiophene, furan, thienopyridine, pyridine, pyrimidine, pyrazine, triazine, imidazole, thiazole, oxazole, indole, azaindole, thioindole, oxindole, purine, quinoline or isoquinoline; wherein optionally substituted imidazole is not 4-(4-flurophenyl)-1(1-methylpiperdin-4-yl)imidazole;

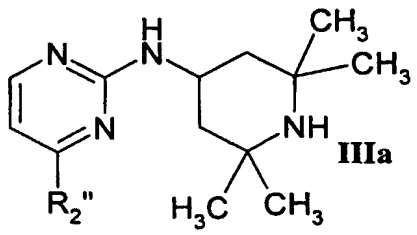
each R3' and R4' is independently H, CN, halo, hydroxy, lower alkyl or lower alkoxy;

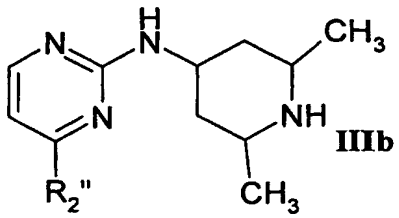
each of R8', R9', R10' and R11' is independently H, lower alkyl, lower alkoxy, -CH$_2$-O-Rx, -C(O)-Rx, -O-C(O)-Rx, -S(O)-Rx, , -O-S(O)-Rx, -CH$_2$-O-Rx or –NH-C(O)-Rx, where Rx is as defined above;

wherein at least 1 of the substituents R8' to R11' is not equal to H; or R8 and R10 are both H and R9 and R11 are joined to form an optionally substituted C_1 to C_4 bridge in which one or more of the bridge atoms is optionally replaced by O, S or NRy, where Ry is H or optionally substituted lower alkyl, -C(O)-Rx, -O-C(O)-Rx, -S(O)-Rx, , -O-S(O)-Rx, -CH$_2$-O-Rx or –NH-C(O)-Rx, where Rx is as defined above

or a pharmaceutically acceptable salt, ester or prodrug thereof.

3. A compound according to claim 1 of formula IIIa or IIIb or a pharmaceutically acceptable salt, ester or prodrug thereof


IIIa


IIIb

wherein

R2" is optionally substituted phenyl, thiophenyl, benzthiophenyl, pyridinyl, naphthalenyl or indolyl aryl (including heteroaryl),

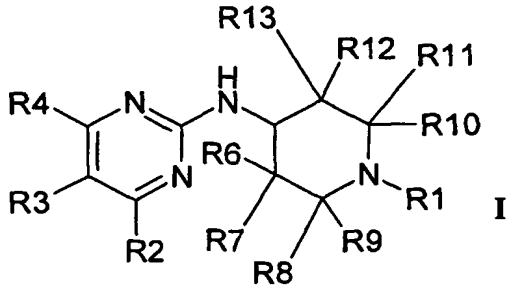
wherein R2'' is optionally substituted by one or more substituents R20 independently selected from OH, halogen, CN, NO_2, or optionally substituted (lower alkyl (including cycloalkyl), lower alkene, lower alkyne, lower alkoxy, lower alkenyloxy, lower alkynyloxy, aryl, heteroaryl or heterocycloalkyl, NH_2 (optionally mono- or disubstituted by lower alkyl, aryl, heteroaryl, aryl-lower alkyl, heterocycloalkyl or heterocycloalkyl-lower alkyl), or -C(O)-Rx, -O-C(O)-Rx, -S(O)-Rx, -$S(O)_2$-Rx, -CH_2-O-Rx or –NH-C(O)-Rx, where Rx is as defined above),

wherein R20 is optionally substituted by one or more substituents R21 independently selected from OH, halogen, CN, NO_2, or optionally substituted (lower alkyl (including cycloalkyl), lower alkene, lower alkyne, lower alkoxy, lower alkenyloxy, lower alkynyloxy, aryl, heteroaryl, heterocycloalkyl, NH_2 (optionally mono- or disubstituted by lower alkyl, aryl, aryl-lower alkyl, heterocycloalkyl or heterocycloalkyl-lower alkyl), or -C(O)-Rx, -O-C(O)-Rx, -S(O)-Rx, -O-S(O)-Rx, -CH_2-O-Rx or –NH-C(O)-Rx, where Rx is as defined above), and

wherein R21 is optionally substituted by one or more substituents R22 independently selected from OH, halogen, CN, NO_2, or lower alkyl (including cycloalkyl), lower alkoxy, aryl, heteroaryl, or heterocycloalkyl, NH_2 (optionally mono- or disubstituted by lower alkyl, aryl, aryl-lower alkyl, heterocycloalkyl or heterocycloalkyl-lower alkyl), or -C(O)-Rx, -O-C(O)-Rx, -S(O)-Rx, -O-S(O)-Rx, -CH_2-O-Rx or –NH-C(O)-Rx, where Rx is as defined above).

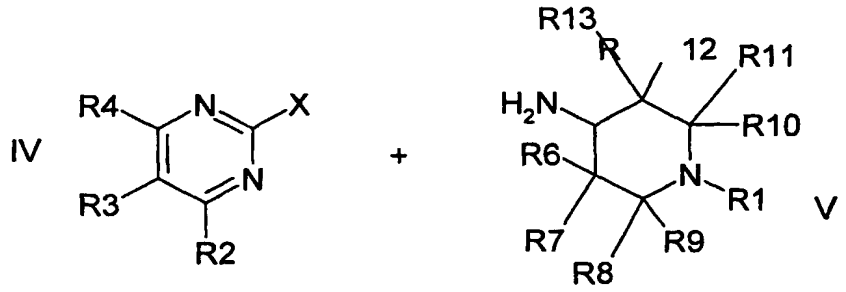
4. A compound selected from the compounds of Examples 1 to 226 and pharmaceutically acceptable salts, esters or prodrugs thereof.

5. A process for the preparation of an Agent of the Invention of formula I



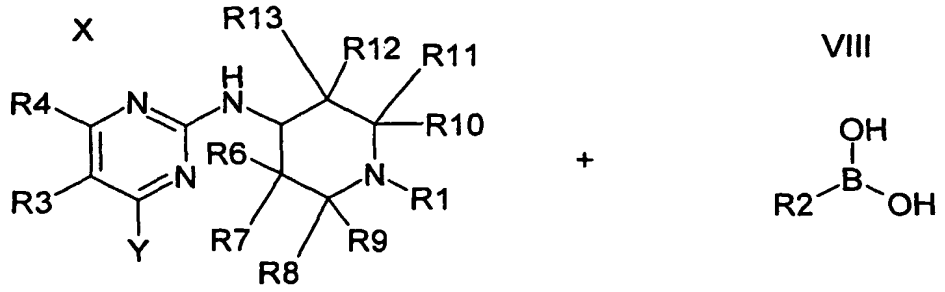
wherein the R substituents are as defined above, comprising

(i) coupling of a pyrimidine derivative of formula IV, e.g. chloro-pyrimidine, methanesulphonyl-pyrimidine or methanesulphinyl-pyrimidine with a piperidin-4-ylamine of formula V



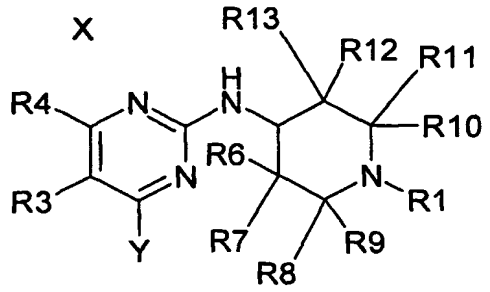
wherein the R substituents are as defined above and X is halo, $-SO-CH_3$ or $-SO_2-CH_3$;

(ii) coupling of a (4-halo-pyrimidin-2-yl)-piperidin-4-yl-amine of formula VII with a aryl boronic acid of formula X



wherein the R symbols are as previously defined and Y is halo, or

(iii) for the preparation of an Agent of the Invention of formula I wherein R2 is N-heteroaryl attached to the pyrimidine ring via an N-atom, coupling of a (4-halo-pyrimidin-2-yl)-piperidin-4-yl-amine of formula X



wherein the R symbols are as previously defined and Y is halo, e.g. Cl, with the alkali metal salt, e.g. sodium or potassium salt, of the N-heteroaryl compound.

6. A method of inhibiting IKK activity in a patient suffering from an IKK mediated disease which comprises administering to the patients an effective amount of a compound according to claim1.

7. A method of inhibiting production of TNF, especially TNFα, IL-1, COX-2, or other inflammatory mediators, or of reducing inflammation in a subject (i.e., a mammal, especially a human) in need of such treatment which method comprises administering to said subject an effective amount of an Agent of the Invention, or a method of treating any of the above mentioned conditions, particularly a method of treating an inflammatory or autoimmune disease or condition, e.g. rheumatoid arthritis, treatment of cancer, prevention of organ rejection or alleviating one or more symptoms of any of the above mentioned conditions.

8. An Agent of the Invention for use as a pharmaceutical, e.g. for use as an immunosuppressant or antiinflammatory agent or for use in the prevention, amelioration or treatment of any disease or condition as described above, e.g., an autoimmune or inflammatory disease or condition.

9. A pharmaceutical composition comprising an Agent of the Invention in association with a pharmaceutically acceptable diluent or carrier, e.g., for use as an immunosuppressant or

anti-inflammatory agent or for use in the prevention, amelioration or treatment of any disease or condition as described above, e.g., an autoimmune or inflammatory disease or condition.

10. Use of an Agent of the Invention in the manufacture of a medicament for use as an immunosuppressant or anti-inflammatory agent or for use in the prevention, amelioration or treatment of any disease or condition as described above, e.g., an autoimmune or inflammatory disease or condition.

11. All novel compounds, processes, methods and uses substantially as hereinbefore described with particular reference to the Examples.